33

CHRONIC LEAD NEPHROPATHY IN QUEENSLAND: ALTERNATIVE METHODS OF DIAGNOSIS

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Abstract:

Indices of past lead absorption were measured and compared in patients with chronic renal failure from many causes, including some with chronic lead nephropathy. X-ray fluorescence (XRF) yielded finger bone lead concentrations by a new *in vivo* method. These correlated significantly with excess urinary lead following calcium di-sodium EDTA (ethylenediamine tetra-acetate) and erythrocyte lead concentration.

Discriminant function analysis demonstrated that the patients in the study could be separated into two groups without any reference to the EDTA lead excretion test using the following variables, all of which contributed significantly to the discrimination. In order of importance, these were: a childhood history of acute lead poisoning, a history of gout, a family history of gout and detectable XRF finger bone lead.

Although the XRF finger bone lead measurement is convenient and non-invasive, its lack of sensitivity (48%) limits its usefulness as a screening test for chronic lead nephropathy. (Aust NZ J Med 1986; 16: 11-19.)

Key words: **Lead poisoning, kidney, x-ray fluorescence, EDTA, gout.**

The incidence of "chronic nephritis" amongst young people in Queensland was noticed to be greater than that in the other Australian states in 1929.[1] This increased incidence led to increased mortality from chronic renal disease, which Henderson, in 1958, concluded was due solely to lead absorption in childhood.[2] With Inglis he suggested that bone lead content could be used in cases of "chronic Bright's disease" as a valid indication of excessive lead absorption.[3] Using the criteria of Henderson and Inglis (bilateral symmetrically contracted kidneys and bone lead concentration >50 μg/g, ash weight), Searle *et al.* discovered 23 cases of lead nephropathy at autopsy in 1900 patients at the Royal Brisbane Hospital in the five year period 1975 to 1980, and therefore concluded that chronic lead nephropathy continues to contribute to morbidity and mortality in Queensland.[4] That report[4] also included an additional 11 patients with a diagnosis of lead

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nephropathy based on a positive lead excretion test.

The calcium disodium EDTA (ethylenediamine tetra-acetate) lead excretion test is regarded as the most reliable clinical method for demonstrating excessive past lead absorption.[7,8] A newer, non-invasive, and less time-consuming method is that of x-ray fluorescence (XRF) which measures *in vivo* the lead concentration in bone.[9] We have measured XRF finger bone lead concentrations in 200 apparently healthy Queensland adults and found significant correlations between childhood residence in a painted wooden house and raised lead levels, and between occupational exposure to lead and raised lead levels.[10]

The following criteria for a diagnosis of chronic lead nephropathy during life were proposed by Emmerson in 1973:[11] (1) features of a longstanding, slowly progressive chronic renal disease, (2) a moderate to considerable degree of uniform contraction of both kidneys, (3) definite evidence of excessive past lead absorption, and (4) the exclusion of alternative causes of chronic renal failure.

The evidence for excessive past lead absorption was based on an abnormal increase in the urinary excretion of lead after a standardised infusion of calcium disodium EDTA[12] and/or a substantiated history of acute lead poisoning in the patient or a sibling. Some of Emmerson's cases were mentally retarded[13] and more than half had gout.[11]

This study seeks to evaluate the contribution variables other than the EDTA lead excretion test might make to the diagnosis of lead nephropathy, in particular a history of childhood lead exposure, gout, XRF finger bone lead concentration, blood lead concentration and tests of psychological function, namely problem solving and vocabulary. In addition, as lead is stored in the skeleton,[3] plasma concentrations of parathyroid hormone (iPTH), 25-hydroxycholecalciferol, and alkaline phosphatase were measured in order to determine whether any of these indices of bone cell activity correlated with any of the measurements of the body burden of lead.

PATIENTS

The patient sample consisted of 39 patients (12 men, 27 women; age range 48-77 years), whose plasma creatinine concentrations ranged from 0.13 to 1.58 mmol/l. All attended the Renal Clinic of the Royal Brisbane Hospital and gave written informed consent.

The patients were divided into two groups. At the commencement of the study, 19 patients were considered to have chronic lead nephropathy ("lead group") using Emmerson's criteria.[11] All had excessive past lead absorption shown by a positive EDTA test (>2.9 μmol of EDTA lead excess).[12] Ten had a history of acute lead poisoning in either the patient (eight cases) or a sibling (two cases). Fifteen gave a history of at least one episode of acute gout, consisting invariably of acute mono-articular arthritis of the first metatarsophalangeal joint. Six had a family history of gout. The four males and 15 females ranged in age from 51 to 77 years (mean 62.8 ± 6.4SD) and had plasma creatinine concentrations between 0.18 and 0.98 mmol/l (mean 0.5 ± 0.23).

Twenty patients not considered to have lead nephropathy on clinical grounds acted as controls. Eight patients had the typical radiological findings of analgesic nephropathy of scarred kidneys with calyceal deformity consistent with papillary necrosis and, in addition, admitted to the consumption of more than 3 kg of phenacetin (in the form of compound powders containing aspirin, phenacetin and caffeine) over a period of more than five years. Other renal diagnoses included one case of athero-embolic disease, two cases of renal calculous disease, two cases of chronic pyelonephritis, and seven cases of chronic glomerulonephritis. These five diagnostic categories comprised the "non-lead group".

In the non-lead group there were eight males and 12 females. These patients had the following clinical characteristics: mean age 60.5 ± 6.3 years (range 48 to 68) and plasma creatinine concentration 0.61 ± 0.4 mmol/l (range 0.13 to 1.58). Only one of the 20 patients had a history of possible childhood lead exposure (a sibling with plumbism). Eight patients (one with analgesic nephropathy) had had previous attacks of acute gout. One of the 20 patients had a family history of gout.

All 39 patients had blood taken for measurement of whole blood lead concentration and various biochemical and endocrine parameters within one month of XRF finger bone lead measurement and psychological assessment.

METHODS

EDTA lead excretion test

The EDTA test was performed as follows: 24 hour urinary lead excretion was measured on each of six consecutive days with 1 gram of EDTA given intravenously in 250 ml of 5% dextrose over one hour, six hours into day 3. Excess lead excreted was calculated by subtracting twice the amount excreted on control days 1 and 2 from the sum excreted on days 3, 4, 5, and 6. In the presence of renal failure the excretion of the lead chelate is delayed, but the amount of excess lead remains less than 2.9 μmol in unexposed persons.[12]

Bone lead detection system

The bone lead detection system uses x-ray fluorescence (XRF). The system when used for the *in vivo* detection of skeletal lead relies on the detection of characteristic x-rays excited by 122 keV photons emitted from Co-57 sources, as described by Ahlgren and Mattsson.[9] The Brisbane system uses two Co-57 sources in a bilateral arrangement and a 13.5% Ge(Li) detector.[10] The measurement involves irradiation of the middle phalanx of the index finger, which is clamped in a positioning jig for a period of 1000 seconds. Lead concentration is standardised using results from finger-like phantoms containing known concentrations of lead. The absorbed dose is approximately 5 mGy (500 mrad) to the 1 cm^3 volume of the finger irradiated; whole body and gonad doses are negligible. Our technique enables the level of lead to be determined with a minimum detection limit of 25 μg/g for 1000 seconds of irradiation time.

As there was no quantitative assessment of bone lead below the *minimum detectable limit*, the variable XRF was, in statistical terms "censored". With the method of Cohen,[14] after assuming an approximation to a lognormal distribution for bone lead, estimates of the distribution were derived from the non-censored observations. This allowed the calculation of the expected value for the unknown determinations. This quantity was found to be 10.7 μg/g; thus observations initially recorded as "not detectable" were subsequently assigned the value of 10.7 for the purpose of the discriminant analysis.

Biochemical methodology

All lead determinations in urine and blood were made with a Varian Techtron Model AA6 atomic absorption spectrophotometer equipped with a Carbon Rod Atomiser Model 63. Blood for measurement of whole blood lead was collected into lithium heparin and later hemolysed with saponin. As 95% of lead in blood is bound to erythrocytes,[15] it was considered necessary to express the blood lead concentration as μmol per unit of hematocrit (erythrocyte lead). Plasma creatinine and alkaline phosphatase concentrations were determined by standard "Technicon" SMAC procedures. Serum parathyroid hormone (i-PTH) concentration was measured by a radio-immunoassay which recognises both the COOH-terminal and the NH_2-terminal.[16] Serum 25-hydroxyvitamin D concentration was measured by a competitive protein binding assay.[17]

Psychological testing

Intellect was assessed using Raven's Progressive Matrices (RPM) as a test of problem solving capacity and the Peabody Picture Vocabulary Test (PPVT) as a test of vocabulary. These tests were chosen because they are reliable, simple, and quick. Results were expressed throughout as units of IQ.

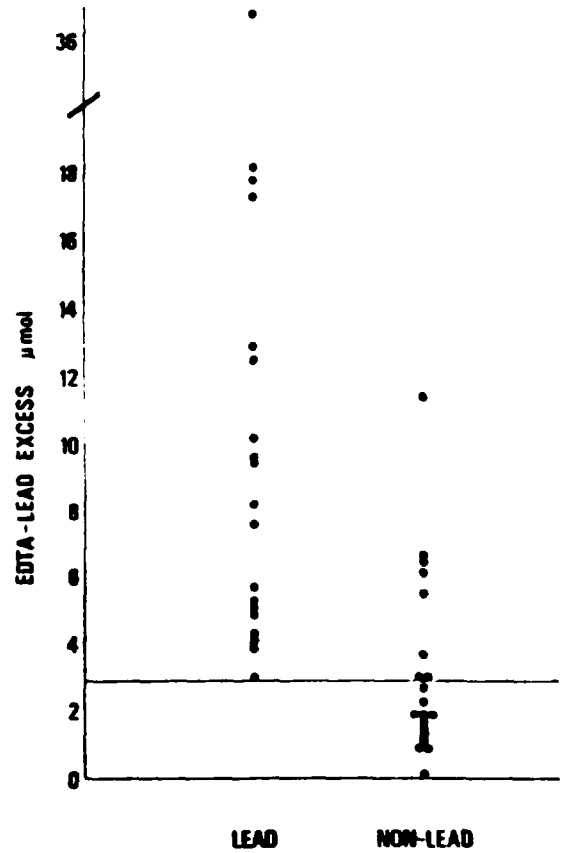

Figure 1: EDTA-lead excess in the three patient groups; 2.9 μmol is considered the upper limit for normals.

Statistical methods

Values were expressed as mean ± standard deviation. Data were analysed by Student's *t*-test, the Mann-Whitney U test and the chi-squared test. Pearson product moment correlation coefficients were also calculated to examine associations among variables. The discriminant function analysis was carried out using the Statistical Package for the Social Sciences.[18]

RESULTS

Group analyses

EDTA lead test

All 19 patients in the lead group and eight of 20 in the non-lead group (Fig. 1) excreted more than 2.9 μmol of excess lead following EDTA. The mean

TABLE 2
Pearson Correlation Coefficients (r) between Lead Measures and Plasma Alkaline Phosphatase

	Erythrocyte lead	$n = 39$ EDTA lead	XRF lead	Alk phos.
Erythrocyte lead	1.0			
EDTA lead	0.61***	1.0		
XRF lead	0.40**	0.50**	1.0	
Alk. Phos	0.38**	0.74***	0.39**	1.0

*$p < 0.05$, **$p < 0.01$, *** < 0.001.

discriminant in the first place, a further analysis of variables was carried out. Table 3 depicts the results of the discriminant function analysis.

The order of importance of the variables being considered can be determined by the absolute values of the standardised discriminant function coefficients (SDFC). Such coefficients, ignoring sign, were, in decreasing order, lead poisoning in childhood, history of gout, family history of gout and XRF.

Other variables which contributed to the discrimination were, in order, RPM units, plasma creatinine levels, and the sex of the patient. Once these seven variables were taken into account, little extra discrimination remained.

It is interesting to note that PPVT and erythrocyte lead, initially significant, diminished in importance as discriminants, once the childhood history of lead poisoning was considered.

Wilks' lambda is a measure of the discriminating power left in the other variables. Thus, the smaller the lambda is, the greater the degree of discrimination attributable to the variables. Levels for the initial significance (third column of Table 3) were evaluated by t-test and chi-squared test, whichever was appropriate. Wilks' lambda for the entire set of variables in Table 3 was 0.32, indicating a high level of discrimination.

Using these results, the 19 patients in the lead group were all classified as "lead" and the 20 in the non-lead group 18 as "non-lead". Overall, in 95% of cases discriminant function classification and clinical classification were in agreement.

Table 3 also gives the unstandardised discriminant function coefficients (U/S DFC). By multiplying an individual patient's scores by these factors and by adding a constant (−4.457), discriminant scores can be determined. Calculated on this basis, the group centroids were, for the lead group, −1.480 and for the remainder 1.406.

To test this approach the following example is considered: Patient No. 3 has a history of lead poisoning in childhood and a history of gout, no family history of gout, the XRF finger bone lead concentration is 128 μg/g, his RPM score is 78, and the plasma creatinine concentration is 0.51 mmol/l. His score is determined by summing the items of Table 3. The components in order are $2.157 + 1.667 + 3.83 - 2.304 - 4.118 + 0.536 - 0.733 - 4.457 = -3.422$. This puts him below the cut-off point for the discriminant function (−0.037) and indicates a diagnosis of lead nephropathy. The cut-off point is the mid point between the two centroids.

As a further check on the efficacy of this diagnostic approach, ten new patients who had not had an EDTA lead excretion test were classified. These patients comprised seven cases of analgesic nephropathy, two of chronic pyelonephritis and one

TABLE 3
Results of Discriminant Function Analysis

Variable	Initial Discrimination: Wilks' lambda	Initial Discrimination: Significance	Final Discriminant Function: *SDFC	Final Discriminant Function: †U/S DFC
Lead poisoning in childhood (Yes = 1, No = 2)	0.72	0.001	0.845	2.157
History of gout (Yes = 1, No = 2)	0.84	<0.01	0.773	1.667
Family history of gout (Yes = 1, No = 2)	0.88	<0.05	0.708	1.915
XRF (μg/g; 10.7 = ND)‡	0.78	0.003	−0.505	−0.0180
RPM (IQ units)	0.99	NS**	−0.399	−0.0528
Creatinine (mmol/l)	0.97	NS	0.348	1.051
Sex (1 = M, 2 = F)	0.96	NS	−0.339	−0.733
Constant				−4.457

*SDFC = Standardised Discriminant Function Coefficients; †U/S DFC = Unstandardised Discriminant Function Coefficients; ‡ND = Not detectable; **NS = Not significant.

case of chronic glomerulonephritis. All were classified as "non-lead", in accordance with the clinical diagnosis.

The discriminant function analysis was repeated, this time including the EDTA lead excretion test results. While the EDTA test produced highly significant differences between the lead and non-lead groups, it contributed no additional discriminating power after the seven variables in Table 3 were taken into account.

DISCUSSION

The EDTA lead test is cumbersome and requires the careful collection of six days' urine, an intravenous route of administration, and a laboratory skilled in trace metal analysis. We confirmed previous observations[5,12] that a four-day period of urine collection following EDTA may not be sufficient for levels of lead to return to baseline and that the peak level may be delayed from day 3 to day 4 or to day 5 of the six-day test period. Some workers have tried to simplify the test by giving the calcium disodium EDTA orally[19] or intramuscularly,[7] by omitting the baseline urine collection,[6,7,19] and by reducing the period of urine collection following EDTA from four days[12] to three[7] or even one.[6]

It is necessary to explain why three of eight patients with analgesic nephropathy and five of 12 patients with other causes than lead or analgesic nephropathy for their renal failure excreted more than 2.9 μmol of excess lead, the upper limit of normal used by both Emmerson[5,12] and Wedeen.[7] It is possible that the patients had more than one disease causing their renal failure. In support of this, houses in Queensland were almost entirely built of wood and in the past were painted exclusively with lead paint.[1] Children brought up in Queensland in the first three decades of this century were thus raised in an environment with a high level of lead. In addition, Queensland has one of the highest rates of analgesic abuse of the six Australian States.[20] Emmerson[5] found elevated EDTA lead excretion in four of 23 patients with chronic renal disease attributable to causes other than childhood lead poisoning. He considered that his patients had undergone unrecognised but excessive lead absorption in the past, unrelated to their disease.

Three of our patients (14, 15, and 26) came to autopsy. The original diagnoses were confirmed (athero-embolic disease in patient 14 and analgesic nephropathy in patients 15 and 26). The bone lead concentration was elevated (95 μg/g and 60 μg/g ashed bone; normal range for skull 30-50 μg/g) in patients 14 and 26, confirming excessive past lead absorption. Patient 15 had a skull bone lead concentration of 15 μg/g ashed bone. However, the patient may have been able to mobilise lead from her bones during the ten months before her death when she had a functioning cadaveric renal transplant.

All of the remaining five patients with positive EDTA lead excretion tests in the non-lead group had causes other than chronic lead poisoning for their renal insufficiency. Patient 7 has had surgery for the removal of renal calculi and a parathyroid adenoma. Patient 13 has also had a parathyroid adenoma removed and, in addition, has all the criteria mentioned previously for a diagnosis of analgesic nephropathy. Patient 17 has had intravenous pyelograms in Plymouth, England, and in Brisbane which demonstrate bilaterally scarred kidneys with dilated calyces. Patient 27, unlike patient 24, has had a renal biopsy which showed an end-stage kidney consistent with chronic glomerulonephritis. Patients 17 and 24 were born and raised outside Australia (England and Hungary). The remaining six patients with positive EDTA lead excretion tests were born and raised in Queensland and 27% of symtomless Queensland adults over 50 years of age have XRF finger bone lead levels in excess of 25 μg/g.[10]

Childhood lead exposure in the patient or in a sibling proved to be the most significant discriminant, with ten of 11 patients having a positive EDTA lead excretion test. Henderson followed 401 cases of plumbism in Queensland children and concluded that the original diagnosis of plumbism was probably correct in most cases.[21]

Gout was the next most significant discriminant after lead exposure in childhood. Fifteen of the 19 patients in the lead group had gout, compared with eight of 20 in the non-lead group. In addition, 19 of the 23 patients with gout had positive EDTA lead excretion tests. These findings confirm previous reports, some of which date back to the late nineteenth century,[12,22-25] that gout may be a useful marker of chronic lead poisoning. As a family history of gout was the next most significant discriminant, this suggests that other members of the family may unknowingly have ingested lead.

The patients in the lead group had significantly lower scores on the PPVT, consistent with the hypothesis that lead exposure in childhood had impaired their acquisition of vocabulary. That damage induced by lead leads to brain damage (in particular calcification in the cerebellum and basal ganglia) and that such patients may have raised bone lead levels was reported by Tonge *et al.*[26] using autopsy material from Queensland. Such patients characteristically fail to achieve high occupational status.[27] RPM emerged as contributing to the discriminant function, low RPM indicating lead

group status. There was a significant positive correlation between RPM and plasma creatinine ($r = 0.343$, $p = 0.016$). This was unexpected because one would expect problem solving capacity to fall as renal function worsens.[18] The likely explanation for this is that the mean plasma creatinine was lower in the lead group and that group status had an overriding effect.

Bone biopsy[29] and/or bone marrow lead concentration[10] have not been used widely as diagnostic tests for lead poisoning because of their invasive nature. The non-invasive XRF technique has the advantage of simplicity and speed of operation. We identified 16 out of 39 uremic patients as having detectable finger bone lead (mean 56 ± 34 μg/g; range 25 to 128) with more from the lead group. These levels were comparable with those reported by Ahlgren and Mattson in retired metal workers[9] and industrial workers.[31] However, our XRF method failed to detect lead in 14 of 27 patients with a high result for the EDTA test. This lack of sensitivity may be explained by the non-uniform distribution of lead in the skeleton. Certainly, bone from the skull[1] and tibia[32] has a higher content of lead than rib bone both in normal subjects and in patients with lead nephropathy. In addition, secondary hyperparathyroidism would be expected to increase further the turn-over of bone and not uncommonly leads to sub-periosteal erosions and cyst formation in the bones of the fingers. For this reason, finger bone may not have been the ideal bone to use.

The whole blood lead concentration correlated positively with the XRF finger bone lead concentration and the excess lead excreted following one gram of EDTA given intravenously. In our patients with chronic renal failure, the erythrocyte lead concentration, a better guide than whole blood lead, gave even stronger correlations with both XRF and EDTA results. A similar relationship between erythrocyte lead and EDTA excess lead has been found in German patients with chronic renal failure (Eberhard Ritz, personal communication). In other studies, whole blood lead concentrations have either not correlated significantly with EDTA lead values[10] or have correlated only in workers with recent exposure.[33] None of our patients had been exposed recently to lead. Indeed, the highest whole blood lead concentration in our patients was 1.1 μmol/l, which is well below the lead level of 3.9 μmol/l recommended as an upper limit delineating acceptable from unacceptable lead absorption in industrial workers,[34] and also below the level of concern for the Australian population of 1.4 μmol/l set by the National Health and Medical Research Council of Australia in 1979.[35]

Discriminant function analysis demonstrated that the patients in the study could be separated into two groups without any reference to the EDTA lead test using the following variables: a childhood history of lead poisoning, a history of gout, a family history of gout, and the concentration of lead in finger bone as measured by XRF. All of these variables contributed significantly to the discrimination.

Finally, lead nephropathy continues to contribute to morbidity and mortality in Queensland, but Henderson's prediction[36] suggests that it will disappear from the community between 1990 and 2000.

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BOOK REVIEW

NEUROCARDIOLOGY. THE INTERRELATIONSHIPS BETWEEN DYSFUNCTION IN THE NERVOUS AND CARDIOVASCULAR SYSTEMS. By John Walton. Major Problems in Neurology, Vol. 13. Consulting editors Ralph H. Johnson, David G. Lambie, and John M. K. Spalding. WB Saunders, 1984. Recommended retail price £19.50 (hardback). ISBN: 0-7216-1375-6.

This book examines the inter-relationships between dysfunction in the nervous and cardiovascular systems. It is divided into three major sections. The first gives a good overview of the nervous control of the circulation. In the second section, neurogenic abnormalities of the heart, neurogenic hypertension, orthostatic hypotension, syncope without heart disease, and the role of emotion and pain are considered. In the final section, the effects of the cardiovascular system on the nervous system are considered including heart disease and syncope, cerebral blood flow, strokes, problems with spinal cord, vascular headaches, and systemic disorders of blood vessels. This book can be thoroughly recommended to neurologists, cardiologists and general physicians. Each subject is gone into in considerable detail and many references are included. One minor criticism, which results from the way the book is sectioned, is that some single subjects have to be chased through various subsections to gain a complete overview. At approximately £20 it is excellent value for money.

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